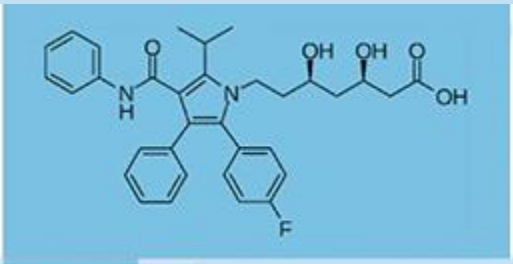
IAS STATIN NEWSLETTER



INTERNATIONAL ATHEROSCLEROSIS SOCIETY

A CURATED WEEKLY UPDATE OF ALL STATIN PUBLICATIONS

Update - Week 30, 2021

**Curated by Peter Lansberg,
a Dutch lipidologist and educator, and
reviewed by prof. Philip Barter, Past President of the
International Atherosclerosis Society.**

The IAS statin literature update will keep you up-to-date with all recent statin publications, using a curated approach to select relevant articles.

Key publications

Premature atherosclerosis insufficiently recognized and managed

Premature atherosclerosis (PAS) is diagnosed if individuals have manifestations of CAD before the age of 50 in males and females before 55 years. Strategies to prevent PAS are underserved in current updated guidelines. Based on data collected in the Study to Avoid CardioVascular Events in British Columbia (SAVE BC), PAS patients were evaluated. CAD was defined as angiographically-confirmed CAD with stenosis of >50% in at least one coronary artery in patients presenting with the first STEMI, NSTEMI, unstable or stable angina, or referred electively for angiography. Included in the analysis were 417 patients (28.1% females). Almost all patients (94.3%) were found to have at least one of six major

CVRFs: dyslipidemia (68.6%, including 14.1% of patients with LDL-C ≥5 mmol/L), hypertension (47.0%), family history of premature CVD (40.8%), obesity (40.6%), current smoking (26.9%), or diabetes (26.9%). Based on guideline recommendations from the American College of Cardiology/American Heart Association, Canadian Cardiovascular Society, and European Society of Cardiology guidelines, 47.7%, 61.4%, and 34.3%, respectively, were eligible for statin therapy. Statins were used by 17.1%, and only 11.0% achieved guideline-recommended LDL-c targets. increased plasma lipids and diabetes showed a positive association with statin use; smoking was associated with non-treatment. These findings warrant new effective strategies and guidelines to improve screening and management strategies for premature CAD.

Vikulova DN, Skorniakov IS, Bitoiu B *et al.* Lipid-lowering therapy for primary prevention of premature atherosclerotic coronary artery disease: Eligibility, utilization, target achievement, and predictors of initiation. Am J Prev Cardiol 2020; 2:100036.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34327459

PCSK9ab associated with renal side effects

In the recently updated ACC/AHA lipid management guidelines, the addition of PCSK9ab has been recommended (Class IIa) for high-risk patients that show insufficient LDL-c lowering response to maximally tolerated high dose high, intensity statin plus ezetimibe. In the major trials that evaluated the efficacy and safety of PCSK9ab therapy, this class of drugs has shown an excellent safety profile. In this case report, a patient with advanced renal disease and statin intolerance developed an acute tubular injury, confirmed with renal biopsy after PCSK9ab were initiated. Stopping the therapy resulted in creatinine clearance returning to baseline levels. This rare side effect was reported in only two other case reports, one patient with advanced renal disease and a patient with normal renal function. The potential mechanism causing renal harm remains elusive; potentially, emollients of the injectable drug could be responsible for the renal effects. PCSK9ab are considered as a very safe injectable class of drugs; however, with increasing numbers of patients using PCSK9ab real world data will expand, as will the number of novel side effects undetected in the clinical trials due to the rarity of certain adverse events as the one reported in this case report. Being aware of these uncommon adverse occurrences early, can prevent the progression of serious complications.

Pickett JK, Shah M, Gillette M *et al.* Acute Tubular Injury in a Patient on a Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor. JACC Case Rep 2020; 2:1042-1045.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34317411

IVUS progression in patients with absent modifiable risk factors

Do patients in whom common modifiable risk factors are absent show signs of coronary

artery atherosclerosis (AS) and progression of AS. An intriguing question was explored by comparing participants (N=5823) in ten clinical trials that evaluated IVUS imaging to determine the effects of medical therapies on plaque progression. A total of 165 (2.8%) patients were found to have no self-reported common modifiable risk factors (smoking, hypertension, diabetes, and hypercholesterolemia). They were compared with patients with at least one such risk factor after matching (3:1) on age, sex, and use of statins during the trials (N=492). Patients with modifiable risk factors had significantly higher systolic blood pressure, LDL-c, triglycerides, and hsCRP, at baseline. IVUS parameters at baseline were significantly better than in patients with modifiable risk factors. Percent atheroma volume, 35.7 ±8.6 vs. 38 ±8.8% (p=0.004) and total atheroma volume, 174.7 ± 80 vs. 190.9 ± 84 mm3 (p = 0.03) and vascular calcifications were fewer as well, 22.2 vs. 26.5% (p=0.025). The use of aspirin and statin before and during the trials was similar. The percentage of patients that showed progression of atherosclerosis was similar in both groups, 50.9% vs. 45.1% (p=0.20). This analysis showed that even without major, modifiable risk factors, patients did have atherosclerosis, albeit less when compared to those individuals with risk factors. Progression was observed in both groups with no significant difference in the rate of progression.

Mazhar J, Figtree G, Vernon ST *et al.* Progression of coronary atherosclerosis in patients without standard modifiable risk factors. Am J Prev Cardiol 2020; 4:100116.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34327476

Does baseline LDL-c matters when using intensive LDL-c lowering interventions?

This brief report examined critical and clinically relevant questions; What is the impact of baseline LDL-c on observed benefit after intensive LDL-c lowering? Data of 53 RCTs (N=329 897) were evaluated in this meta-analysis. The relevant outcomes studies were cardiovascular mortality and major cardiovascular events (MACE). Patients were stratified according to baseline LDL-c levels. Similar to previous meta-analyses, each 1 mmol/l (38.9 mg/dl) lower LDL-c was associated with a 15% reduced cardiovascular mortality risk, RR: 085 (0.81-0.89); however, this varied by baseline levels of LDL-c (P=0.04 for interaction). Only patients with LDL-c >100 mg/dL showed a decrease cardiovascular mortality risk. The reduction in MACE was independent of baseline LDL-c. When comparing primary or secondary prevention patients, similar outcomes were observed. The authors concluded that current guideline recommendations to aim for >50% LDL-c reduction from baseline are valid and should be enforced in high CVD risk patients. Khan SU, Michos ED. Cardiovascular mortality after intensive LDL-Cholesterol lowering: Does baseline LDL-Cholesterol really matter? Am J Prev Cardiol 2020; 1:100013.
http://www.ncbi.nlm.nih.gov/pubmed/?term=34327454

Comparing the US and European updated Lipid Management Guidelines

Recently both ACC/AHA and EAS/ESC have released new guidelines on lipid management, in 2018 and 2019, respectively. Both added important information from trials designed to reduce LDL-c to lower targets using novel, non-statin lipid-lowering drugs. Interpretation of the evidence is predominantly similar; however, differences might be confusing for those working in clinical practice that seek simple and straightforward answers. This article provides an in-depth comparison of the distinct differences of both guidelines, explains the rationale of these recommendations, and guides health care providers by answering three critical clinical questions: 1. Are ASCVD event rates similar in high-risk primary and stable secondary prevention? 2. Does imaging evidence of subclinical atherosclerosis justify aggressive use of statin and non-statin therapy (if needed) to reduce LDL-C levels below 55 mg/dL as recommended in the ESC/EAS Guideline? And 3. Do LDL-C levels below 70 mg/dL achieve a large ARR in secondary ASCVD prevention? In large the more cautious US approach, incorporating financial burden of novel treatments is the authors preferred choice where non-statins are recommended selectively for the high- and especially the very-high risk patients.

Feldman DI, Michos ED, Stone NJ *et al.* Same evidence, varying viewpoints: Three questions illustrating important differences between United States and European cholesterol guideline recommendations. Am J Prev Cardiol 2020; 4:100117.

http://www.ncbi.nlm.nih.gov/pubmed/?term=34327477

Relevant publications

1. **Zeki Al Hazzouri A, Jawadekar N, Grasset L *et al.* Statins and cognitive decline in the Cardiovascular Health Study: A comparison of different analytical approaches. J Gerontol A Biol Sci Med Sci 2021.**
   http://www.ncbi.nlm.nih.gov/pubmed/?term=34331536
2. **Young RP, Scott RJ. Statins as adjunct therapy in COPD: is it time to target innate immunity and cardiovascular risk? The European respiratory journal 2021; 58.**
   http://www.ncbi.nlm.nih.gov/pubmed/?term=34326175
3. **Woo JS, Hong SJ, Cha DH *et al.* Comparison of the Efficacy and Safety of Atorvastatin 40 mg/ω-3 fatty acids 4 g Fixed-Dose Combination and Atorvastatin 40**

mg Monotherapy in Hypertriglyceridemic Patients Who Poorly Respond to Atorvastatin 40 mg Monotherapy: An 8-Week, Multicenter, Randomized, Double-Blind Phase III Study. Clinical therapeutics 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34332788

4. Tung H, Lin HJ, Chen PL *et al.* Characterization of familial hypercholesterolemia in Taiwanese ischemic stroke patients. Aging 2021; 13:19339-19351. http://www.ncbi.nlm.nih.gov/pubmed/?term=34314377
5. Toth PP. Low-Density Lipoprotein Cholesterol Treatment Rates in High Risk Patients: More Disappointment Despite Ever More Refined Evidence-Based Guidelines. Am J Prev Cardiol 2021; 6:100186. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327506
6. Schwartz GG, Szarek M, Bittner VA *et al.* Lipoprotein(a) and Benefit of PCSK9 Inhibition in Patients With Nominally Controlled LDL Cholesterol. J Am Coll Cardiol 2021; 78:421-433. http://www.ncbi.nlm.nih.gov/pubmed/?term=34325831
7. Patel J, Mehta A, Rifai MA *et al.* Hypertension guidelines and coronary artery calcification among South Asians: Results from MASALA and MESA. Am J Prev Cardiol 2021; 6:100158. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327495
8. Nelson AJ, Puri R, Brennan DM *et al.* C-reactive protein levels and plaque regression with evolocumab: Insights from GLAGOV. Am J Prev Cardiol 2020; 3:100091. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327467
9. Masson W, Lobo M, Barbagelata L *et al.* Prognostic value of statin therapy in patients with myocardial infarction with nonobstructive coronary arteries (MINOCA): a meta-analysis. Acta Cardiol 2021:1-8. http://www.ncbi.nlm.nih.gov/pubmed/?term=34308792
10. Kudinov VA, Torkhovskaya TI, Zakharova TS *et al.* High-density lipoprotein remodeling by phospholipid nanoparticles improves cholesterol efflux capacity and protects from atherosclerosis. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2021; 141:111900. http://www.ncbi.nlm.nih.gov/pubmed/?term=34328100
11. Klimchak AC, Patel MY, Iorga Ş R *et al.* Lipid treatment and goal attainment characteristics among persons with atherosclerotic cardiovascular disease in the United States. Am J Prev Cardiol 2020; 1:100010. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327452
12. Jeong SM, Shin DW, Yoo TG *et al.* Association between statin use and Alzheimer's disease with dose response relationship. Scientific reports 2021; 11:15280. http://www.ncbi.nlm.nih.gov/pubmed/?term=34315986
13. Jackson CL, Ahmad Z, Das SR, Khera A. The evaluation and management of patients with LDL-C ≥ 190 mg/dL in a large health care system. Am J Prev Cardiol 2020; 1:100002. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327446
14. Israel A, Schäffer AA, Cicurel A *et al.* Identification of drugs associated with reduced severity of COVID-19 - a case-control study in a large population. eLife 2021; 10. http://www.ncbi.nlm.nih.gov/pubmed/?term=34313216
15. Gold ME, Nanna MG, Doerfler SM *et al.* Prevalence, treatment, and control of severe hyperlipidemia. Am J Prev Cardiol 2020; 3:100079. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327462

16. Fischer-Rasokat U, Renker M, Bänsch C *et al.* Effects of statins after transcatheter aortic valve implantation in key patient populations. Journal of cardiovascular pharmacology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34321397
17. Fan W, Philip S, Toth PP *et al.* Estimated ASCVD risk according to statin use in US adults with borderline triglycerides: Results from National Health and Nutrition Examination Survey (NHANES) 2007-2014. Am J Prev Cardiol 2020; 3:100087. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327466
18. Duarte JA, de Barros ALB, Leite EA. The potential use of simvastatin for cancer treatment: A review. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2021; 141:111858. http://www.ncbi.nlm.nih.gov/pubmed/?term=34323700
19. Chidambaram V, Ruelas Castillo J, Kumar A *et al.* The association of atherosclerotic cardiovascular disease and statin use with inflammation and treatment outcomes in tuberculosis. Scientific reports 2021; 11:15283. http://www.ncbi.nlm.nih.gov/pubmed/?term=34315941
20. Baum SJ, Rane PB, Nunna S *et al.* Geographic variations in lipid-lowering therapy utilization, LDL-C levels, and proportion retrospectively meeting the ACC/AHA very high-risk criteria in a real-world population of patients with major atherosclerotic cardiovascular disease events in the United States. Am J Prev Cardiol 2021; 6:100177. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327500
21. Zereshkian A, Waserman S. Liver enzyme elevation and eosinophilia with atorvastatin: a case of probable DRESS without cutaneous symptoms. Allergy Asthma Clin Immunol 2021; 17:81. http://www.ncbi.nlm.nih.gov/pubmed/?term=34330325
22. Williams B, Horn MP, Banz Y *et al.* Cutaneous involvement in anti-HMGCR positive necrotizing myopathy. J Autoimmun 2021; 123:102691. http://www.ncbi.nlm.nih.gov/pubmed/?term=34332436
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24. Okunrintemi V, Benson EA, Derbal O *et al.* Age-specific differences in patient reported outcomes among adults with atherosclerotic cardiovascular disease: Medical expenditure panel survey 2006-2015. Am J Prev Cardiol 2020; 3:100083. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327463
25. Nabizadeh F, Balabandian M, Sharafi AM *et al.* Statins and risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. Acta neurologica Belgica 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34322852
26. Laird J, Falk RH, Coyle M, Cuddy SAM. Rhabdomyolysis in the Setting of Concomitant Use of Tafamidis, Atorvastatin, and Amiodarone. JACC Case Rep 2020; 2:2372-2375. http://www.ncbi.nlm.nih.gov/pubmed/?term=34317174
27. Gawey B, Tannu M, Rim J *et al.* Statin-Induced Necrotizing Autoimmune Myopathy. JACC Case Rep 2020; 2:440-443. http://www.ncbi.nlm.nih.gov/pubmed/?term=34317259
28. Elder P, Sharma G, Gulati M, Michos ED. Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease

prevention. Am J Prev Cardiol 2020; 2:100028. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327455
29. Dardano A, Daniele G, Penno G *et al.* Breaking Therapeutic Inertia With Alirocumab in an 80-Year-Old Patient With Severe Hypercholesterolemia: A Case Report. Frontiers in medicine 2021; 8:699477. http://www.ncbi.nlm.nih.gov/pubmed/?term=34307425
30. Carter AR, Gill D, Davey Smith G *et al.* Cross-sectional analysis of educational inequalities in primary prevention statin use in UK Biobank. Heart 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34315717
31. Brånvall E, Ekberg S, Eloranta S *et al.* Statin use and survival in 16 098 patients with non-Hodgkin lymphoma or chronic lymphocytic leukaemia treated in the rituximab era. British journal of haematology 2021. http://www.ncbi.nlm.nih.gov/pubmed/?term=34331461
32. Al Salman M, Ghiasi M, Farid AS *et al.* Oral simvastatin combined with narrowband UVB for the treatment of psoriasis: A randomized controlled trial. Dermatologic therapy 2021:e15075. http://www.ncbi.nlm.nih.gov/pubmed/?term=34327798
33. Correction to: Antihypertensives and Statin Therapy for Primary Stroke Prevention: A Secondary Analysis of the HOPE-3 Trial. Stroke 2021; 52:e526. http://www.ncbi.nlm.nih.gov/pubmed/?term=34310183

Basic Science publications

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2. Ressaissi A, Pacheco R, Serralheiro MLM. Molecular-level changes induced by hydroxycinnamic acid derivatives in HepG2 cell line: Comparison with pravastatin. Life sciences 2021; 283:119846. http://www.ncbi.nlm.nih.gov/pubmed/?term=34324915
3. Oprica M, Iota M, Daescu M *et al.* Spectroscopic studies on photodegradation of atorvastatin calcium. Scientific reports 2021; 11:15338. http://www.ncbi.nlm.nih.gov/pubmed/?term=34321518

4. **Nam GH, Kwon M, Jung H *et al.* Statin-mediated inhibition of RAS prenylation activates ER stress to enhance the immunogenicity of KRAS mutant cancer. J Immunother Cancer 2021; 9.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34330763
5. **Li Z, Zhang J, Xue Y *et al.* Pitavastatin stimulates retinal angiogenesis via HMG-CoA reductase-independent activation of RhoA-mediated pathways and focal adhesion. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 2021; 259:2707-2716.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34328550
6. **Soares DG, Bordini EAF, Bronze-Uhle ES *et al.* Chitosan-Calcium-Simvastatin Scaffold as an Inductive Cell-Free Platform. Journal of dental research 2021; 100:1118-1126.** http://www.ncbi.nlm.nih.gov/pubmed/?term=34315311

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